

## Peer Review File

Article information: <https://dx.doi.org/10.21037/tcr-21-1189>

### Reviewer A

An interesting overview of stereotactic trials on ClinicalTrials.gov with helpful analysis of trends over time and between jurisdictions. The authors may want to consider presenting their analysis without the 2020 data included as only 1 month of data from 2020 was available and the trends they note would hold up if they restricted their results to those years where they had complete data (i.e. up to calendar 2019)

**Reply:** We thank this reviewer for the reminder. We presented the analysis with the data before December 31, 2019, and added some new data by searching the Clinicaltrials.gov again. So all the data, tables and figures were changed. (see Page 2, line 58 and revised Figure 1)

### Reviewer B

Zhang and his colleagues completed a comprehensive study evaluating the characteristics of stereotactic radiotherapy clinical trials registered on ClinicalTrial.gov. It's an interesting analyze and review to better understand the current situation of stereotactic radiotherapy clinical trials. Tables and figures are clear.

Minors:

- In the introduction, authors defined SBRT. They should cite ICRU 91 report and Potters et al. 2010.

**Reply:** We thank this reviewer for the reminder. We cited ICRU 91 report and Potters et al. 2010 in the Introduction (see Page 1, line 40), also cited as References 2-3. (see Page 6, line 244-250)

- In the discussion, more references are needed to define SBRT, to define fractionation scheme etc.

**Reply:** We thank for the reminder. We cite more references (references 2,3,8,9,10,11,12,13,17). (see Page 6, line 244-250, line 261-263; Page 7, line 264-275, line282)

- In the discussion, the authors are talking about SBRT trials with ICI. They should also talk about studies assessing oligo progression and oligo metastatic.

**Reply:** We thank for the reminder. We added some information about studies assessing oligo progression and oligo metastatic. (see Page 4, line 173-175)

- "P=.000" must be written " $p < 0.001$ "

**Reply:** We thank for the reminder. “P=.000” has been written “p < .001”. (see Page 1, line 26-30; Page 4, line 135,143,144,149,150,153)

- Numbers at the beginning of a sentence must be spelled out (line 109, “362”, line 158 “17.7%”).
- Line 226, “so”

**Reply:** We thank for the reminder. We have corrected numbers at the beginning of a sentence. (see Page 3, line 105; Page 4, line 151)

- The layout of the text needs to be redone (problems with spaces after commas, spaces between numbers ...)

**Reply:** We thank for the reminder. We have corrected layout of the text.

### **Reviewer C**

This manuscript describes a review of all stereotactic radiotherapy trials registered on the clinicaltrials.gov trials registry. The authors perform a search on this database for trials related to stereotactic radiotherapy (both body and intracranial), and then review the results with respect to 11 characteristics of the trials. This manuscript has a number of flaws as detailed below, thus I’m not sure that it is adding much to the community.

I’m not quite sure of the aims of this work. In the introduction, it states (line 45-46): “However, the data related to contemporary trials evaluating stereotactic radiotherapy and their ability to advance clinical care do not yet exist.”

I don’t know what “the data related to contemporary trials...” means as an aim. Thus, the aim of the work is quite superficial, and this flows through to the results. The results and analysis do not go into much depth, and the provided information is limited in scope, with likely substantial gaps. A major gap, which is acknowledged at the end of the discussion, that this is a review of a North American database. Therefore, any geographic and funding analysis of the results is heavily skewed towards this.

**Reply:** We thank this reviewer for the reminder. We added some new information in the introduction, “However, previous studies have found that a large amount of clinical trials are failing to complete, and numerous trials are not published for several years after completion. Failed clinical trials resulting in wasting time, effort and resources, also bring risks to trial participation (see Page 2, line 53-56).

So, we added a new aim of this work, “to compare completed and stopped early trials to identify predictors of trial failure” (see Page 1, line 11-12; Page 2, line 60-61).

And we also made much more deeply analysis in the results, see paragraph “Characteristics Associated with Stereotactic Radiotherapy Trial Stopped Early” (see Page 4, line 157-164). We added Table 4 and Table 5 to show the results.

Finally, we added a conclusion “Stereotactic radiotherapy trials with randomized allocation or enrollment patients ≤50 are associated with trials stopped early stop early” (see Page 6, line 230-232).

The discussion is filled with unsubstantiated statements including:

Line 219-221: “Because United States is the most medically developed country in the world, accounted for 41.7% of total health spending (\$8.0 trillion) worldwide in 2016, and with the largest absolute increases in annual per capita (\$4843) between 1995 and 2016.” (You seem to be conflating ‘medically developed’ with spending the most amount of money.)

**Reply:** We apologize for the confusion. We deleted the above wrong discussion (see Page 5, line 209-212).

Line 225-226: “This observation is consistent with that United States is the fastest and most widespread user of new technologies, instruments and drugs in the field of medicine”. No evidence for this provided.

**Reply:** We apologize for the confusion. We deleted the above wrong discussion (see Page 5, line 209-212).

Line 230-231: “Stereotactic radiotherapy trials demand high quality assurance, and usually tend to take longer time to conduct and complete.” The first half is true, what’s the source for the second half?

**Reply:** We apologize for the confusion. We deleted the above wrong discussion (see Page 5, line 213-216).

Specific comments:

Methods:

Which fields were the search terms used in? There are ‘condition or disease’, ‘other terms’, ‘country’ and can be filtered by recruitment status.

**Reply:** We thank for the reminder. We added the search terms, “other terms” (see Page 2, line 66-67).

Page 2, line 53: “ClinicalTrials.gov is the most robust of the international registries for clinical trials” How is ‘robust’ defined? What is meant by this?

**Reply:** We thank for the reminder. We corrected the ‘robust’ to ‘largest’ (see Page 2, line 50).

We might think that ‘robust’ means large, authority and abundant.

Page 2, line 74 states: “radiotherapy trials were then categorized according to cancer type.” However at line 69 it states this as one of the 11 dimensions: “Stereotactic radiotherapy trials were examined on 11 dimensions: cancer type;...”

**Reply:** We thank for the reminder. We deleted the above discrepancy and repetitive

sentence (see Page 2, line 75).

Page 2, line 76-77: “Trials that involved 2 or more cancer types were grouped into a “not specified or multiple” category”. Shouldn’t this just be multiple?

**Reply:** We thank for the reminder. We corrected the “not specified or multiple” to “multiple”

(see Page 2, line 76).

Page 2, line 80-82: “When the interventional model was single group assignment or the number of treatment arms recorded as “1”, the allocation methods (if missing) were designated as nonrandomized” Does this mean if there were more than 1 arms, they were designated as randomized? Even if they weren’t randomized?

**Reply:** We thank for the reminder. There are some missing information in the database of Clinicaltrials.gov. Sometimes the allocation methods may be unknown. If trials were “1 arm”, we can record as “nonrandomized”.

The statistical analysis section says what tests are used, but doesn’t really say what is being compared. This is likely since there’s no clear aims or hypotheses to this work, so it’s hard to describe the tests?

**Reply:** We thank for the reminder. We added statistical analysis in detail, “Characteristics between the 2 periods of time and between different regions were compared.....In order to investigate predictors associated with trial stopped early, Chi-square test was used to compare characteristics of completed and stopped early trials. Variables with  $P < 0.05$  in univariable analysis were further analyzed by multivariable analysis using binary logistic regression.” (see Page 2-3, line 86-91).

## Results

Page 3, line 97: “Of the total 683 trials registered on ClinicalTrials.gov before Jun 26, 2020 by restricting topic,” this wording isn’t quite right, it suggests only 683 trials were registered before Jun 26 2020. Was this 683 that were returned with the keyword search?

**Reply:** We thank for the reminder. We corrected the above discrepancy sentence, “We retrieved 898 trials from ClinicalTrials.gov before Dec 31, 2019 by restricting topic” (see Page 3, line 95-96).

How was ‘elderly’ defined?

**Reply:** We thank for the reminder. We added the definition “elderly (age >65 years)” (see Page 3, line 107-108).

The methods talk about splitting up funding between NIH and industry, but the results talk about NIH and industry sponsorship. Funding and sponsorship are two different things. Which one are you referring to?

**Reply:** We thank for the reminder. We corrected the ‘sponsorship’ to ‘Funding’ (see Page 1, line 20,24; Page 2, line 80; Page 3, line 131; and so on).

Line 113-114: “There were 396 (68.5%) trials conducted in North America. The majority of trials (77.2%)” Does this reflect the fact that clinicaltrials.gov is a North American register?

**Reply:** We thank for the suggest. We added the sentence “which reflects the fact that clinicaltrials.gov is a North American register” (see Page 5, line 210-211).

Page 3, line 121-124: “(4) compared stereotactic radiotherapy with other radiotherapy regimens, such as IMRT or 3D-CRT” Stereotactic radiotherapy can be and is delivered with IMRT and 3D-CRT. Do you mean to say comparison with conventional or hypofractionation?

**Reply:** We thank for the reminder. We corrected the sentence “compared stereotactic radiotherapy with other radiotherapy regimens, such as conventional or hypofractionation” (see Page 3, line 117).

#### Discussion

A large amount of the discussion is repetition of results.

**Reply:** We thank for the suggest. We deleted some repetitive sentence of results in the discussion (see Page 5, line 183-184, 193-194, 198-199, and so on).

186-188: Furthermore, stereotactic radiotherapy with high doses per fraction is more able to exert an abscopal effect than conventional radiotherapy and is the most appropriate modality to be combined with immunotherapy.”

**Reply:** We apologize for this over-statement. We deleted the over-statement of potential efficacy, and described more tenuous, “Furthermore, stereotactic radiotherapy.....However, some studies found no improvement in abscopal effect or survival with the addition of SBRT to immune checkpoint inhibitors.” (see Page 5, line 188-191)

#### **Reviewer D**

This review is relatively superficial, does not offer much (if any) new information, and is missing a large number of references. Other groups have done a better job of putting the trials in context and actually discussed the landmark trials (e.g. SABR-COMET) and current phase III trials (e.g. SABR-COMET-3 & SABR-COMET-10).

**Reply:** We thank this reviewer for the reminder. We added some new information in the introduction, “However, previous studies have found that a large amount of clinical trials are failing to complete, and numerous trials are not published for several years after completion. Failed clinical trials resulting in wasting time, effort and resources, also bring risks to trial participation (see Page 2, line 53-56).

So, we added a new aim of this work, “to compare completed and stopped early trials to identify predictors of trial failure” (see Page 1, line 11-12; Page 2, line 60-61).

And we also made much more deeply analysis in the results, see paragraph “Characteristics Associated with Stereotactic Radiotherapy Trial Stopped Early” (see Page 4, line 157-164). We added Table 4 and Table 5 to show the results.

Finally, we added a conclusion “Stereotactic radiotherapy trials with randomized allocation or enrollment patients  $\leq 50$  are associated with trials stopped early stop early” (see Page 6, line 230-232).

In addition:

1) the English grammar needs editing (e.g. conclusion in abstract)

**Reply:** We thank for the reminder. We have modified our text as advised.

2) line 185-188 is not well supported by data and is an over-statement of potential efficacy of abscopal effect, which is tenuous at best

**Reply:** We apologize for this over-statement. We deleted the over-statement of potential efficacy, and described more tenuous, “Furthermore, stereotactic radiotherapy.....However, some studies found no improvement in abscopal effect or survival with the addition of SBRT to immune checkpoint inhibitors.” (see Page 5, line 188-191)